

DEVELOPMENT AND VERIFICATION OF NEW SOLID DENTAL FILLING TEMPORARY MATERIALS CONTAINING ZINC. FORMULA DEVELOPMENT STAGE

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Abstract: Caries is the most popular problem affecting teeth and this is the reason why so many temporary dental filling materials are being developed. An example of such filling is zinc oxide paste mixed with eugenol, Thymodentin and Coltosol F®. Zinc-oxide eugenol is used in dentistry because of its multiplied values: it improves healing of the pulp by dentine bridge formation; has antiseptic properties; is hygroscopic. Because of these advantages compounds of zinc oxide are used as temporary fillings, especially in deep caries lesions when treatment is oriented on support of vital pulp. Temporary dental fillings based on zinc oxide are prepared *ex tempore* by simple mixing powder (Thymodentin) and eugenol liquid together or a ready to use paste Coltosol F®. Quantitative composition depends mainly on experience of person who is preparing it, therefore, exact qualitative composition of dental fillings is not replicable. The main goal of the study was to develop appropriate dental fillings in solid form containing set amount of zinc oxide. Within the study, the influence of preparation method on solid dental fillings properties like mechanical properties and zinc ions release were examined.

Keywords: dental fillings, tableting, anodic stripping voltammetry, zinc

Although largely preventable, dental caries and periodontal disease are the two biggest threats to oral health, and are among the most common chronic diseases in children and adolescents. Dental caries is the most common chronic disease in children: it is about five times as common as asthma and seven times as common as hay fever in adolescents. Dental caries also affects adults, 90% of people over the age of 20 have some degree of tooth-root decay. Despite the decline in the prevalence of dental caries in children in the western countries, caries in pre-school children remain a problem in both developed and developing countries (1, 2).

Moreover, the most common cause of tooth loss among adults is untreated periodontal disease. Fifty-three million people live with untreated tooth decay in their permanent teeth. Strikingly, one-quarter of adults aged 65 years and older have lost all of their teeth due to untreated oral disease tooth loss

(3). Having in regard duration of treatment, restorative dental material could be divided into two groups: temporary and long-term used. A great number of temporary restorative materials have been used to seal access cavities, including gutta percha, zinc oxide-eugenol (ZOE) cements and their coproducts, zinc phosphate cements, glass ionomer materials and composite resins (4). An example of such fillings at the dental market are ZOE mixed with thymol (Thymodentin®) and Coltosol F® (5-7). Generally, zinc is widely used in dental restoration particularly in temporal fillings (5, 8) while ZOE is used in dentistry because of its multiplied values such as improving healing of the pulp by dentine bridge formation and antiseptic and hygroscopic properties (3, 4). Because of these advantages zinc oxide is used in temporary fillings, especially in deep caries lesions when treatment is oriented on support of vital pulp. However, ZOE has negative

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effects on microtensile bond strength of adhesives to dentin after 24 h of exposure (12). Temporary dental fillings based on zinc oxide are prepared *ex tempore* simply by mixing powder (Thymodentin®) and liquid eugenol together. Coltosol F® is a ready-to-use paste which hardens in the environment of oral cavity with good coronal seal ability (13). In the first case where Thymodentin is being used, quantitative composition depends mainly on experience of person who prepares it. Exact qualitative composition of dental fillings is not replicable (5-7). Despite its obvious advantages there are described cases of allergic reactions caused by dental fillings. They results from the continuous release of a different - depending on the type of filling - elements, as well as the individual sensitivity. There are also described, others like: mucosal lichen planus (14) cases occurring in the oral cavity, palmoplantar pustulosis (15), follicular rash (maculopapular rash) covering a larger area of the body (16, 22), or a case of erythema, edema and lumpy rash all over the body occurring in individuals due to an allergic reaction to zinc released from the four applied dental fillings (8). The main goal of the study was to develop appropriate dental fillings in solid form containing set amount of zinc oxide. Within the study, the influence of preparation method on solid dental fillings properties were examined. In order to check the chemical stability of the dental fillings, analysis of release of Zn(II) from prepared dental fillings was done.

EXPERIMENTAL

Materials and equipments

The materials used were zinc oxide (POCh), eugenol (Merck), Neusilin US2 (Fuji Chemicals), talc, hydroxypropylmethylcellulose (Pharmacoat 603) (Shin Etsu), colloidal silicon dioxide (Cab-O-Sil), calcium phosphate (Pharma-Zentrale GmbH, Germany), Coltosol® F (Coltene, Switzerland), Thymodentin (Chema-Elektromet, Poland). Equipment used: laboratory kneader LK 5 Erweka, Kube mixer KB Erweka (Germany), dryer KCW 100 (Premed, Polska), tableting machine Korsch EK0, hardness tester (VenKel VK200), friabilator (Pharma Test PTF E, Germany), angle of repose apparatus, angle of slight apparatus, texture analyzer EZ-SX (Shimadzu, Japan), a multipurpose Electrochemical Analyzer M161 with the electrode stand M164 (both MTM-ANKO, Poland) equipped with a classical three electrode quartz cell, volume 5 mL, consisting of Controlled Growth Mercury Drop Electrode (CGMDE), as the working electrode, a

double junction reference electrode Ag/AgCl/ 3M KCl with replaceable outer junction (2.5 M KNO₃) and a platinum wire as an auxiliary electrode. The apparatus was connected to a personal computer with EA9 software. Other materials used for zinc ions determination were: four times distilled water with a conductivity of less than 1 µS/cm, (distillation apparatus SZ-97A, Chemland, Poland); HNO₃ (Merck, Suprapur®); a standard stock solution of Zn (prepared by proper dilution of solution with a concentration 1 g/mL OUM-7 Łódź), supporting electrolyte (prepared by dissolving KNO₃ (Merck, Suprapur®) 3M); and a solution for imitating saliva pH 6.7 (0.400 g of potassium dihydrophosphate, disodium hydrophosphate 0.5200 g, 0.6600 g of potassium thiocyanate, 3.0000 g of sodium bicarbonate, 1.4000 g sodium chloride, 0.2600 g of urea, 2.4000 g of potassium chloride, dissolved in quadruple distilled water in a 1 L volumetric flask).

Preparation of temporary solid dental fillings

Development formula was done by dry granulation and wet granulation methods. Regardless on method of preparation each filling contained 90.0 ± 2% zinc oxide. Dry granulation consists of compaction step followed by a milling step (18, 19). Weighted powder preparation was as follows: zinc oxide, calcium phosphate, and colloidal silicon dioxide were mixed together in Kube mixer KB Erweka. Slugging was performed on a single punch tableting machine Korsh EK0 using flat punches (diameter 20 mm). The slugs were manually crushed, talc was added and solid dental fillings were obtained in tableting process.

To obtained solid dental fillings wet granulation was introduced as a second method of preparation (20, 21). The wet granulation formulation composed of zinc oxide, which was wetted using 15% Pharmacoat 603 as a binder solution, magnesium aluminometasilicate, calcium phosphate and talc. The granulate was obtained in laboratory kneader LK 5, dried using KCW 100 dryer, until up to 0.1% weight loss on drying was achieved. To the granulate, magnesium aluminometasilicate and calcium phosphate were added and mixed together. In the final step, talc was added and mixed. Solid dental filling were obtained in tableting process.

The compressed dental fillings obtained by both dry and wet granulation were prepared during tableting process using single punch tableting machine Korsh EK0 equipped with flat punches (4 mm diameter), tablet weight was 60 mg. They were also characterized by required physical properties that allowed manual crushing just before mixing

with set amount of eugenol and application into teeth.

For comparison purposes of zinc ions release, ready to use temporary dental fillings: Coltosol® F and Thymodentin were manually compressed into tablet shape dental filling. They characterized the same shape, diameter and weight as fillings prepared by dry and wet granulation process.

Testing of final mixtures and solid dental fillings

Properties of final mixtures and temporary solid dental fillings obtained in tableting process were verified by application of appropriate methods. Bulk and tapped density, as well as angle of repose were determined according to Polish Pharmacopoeia (FP X) procedures. Weighted amount of final mixtures was load into 100 mL volume cylinder. Bulk density was calculated as a mass of powder divided by the bulk volume, expressed in g/cm³. Tapped density of final mixtures was determined by filled 100 mL volume cylinder, mounted on a tapping platform and tapped until constant height was obtained. The parameter is expressed in g/cm³ as a mass of powder divided by volume after tapping. Based on bulk and tap density measurement results, Hausner ratio and compressibility index were calculated based on the following equations:

Hausner ratio = tapped density / bulk density

Compressibility index = $100 \times$

$(\text{tapped density} - \text{bulk density}) / \text{tapped density}$

Angle of repose is a three dimensional cone like angle formed by the material during determination. It was calculated after the final mixture was passed through sieve on the polished surface 60 mm diameter. Angle of slight is defined as the angle to

which a polished metal plate must be tilted of powder to start sliding down the plate.

The physical characteristics, hardness and friability of obtained solid dental fillings were also verified according to Polish Pharmacopoeia (FP X) procedures. Hardness was determined by measuring of 10 dental fillings using hardness tester apparatus VenKel VK200. Friability was determined by introduction of 6.5 g of dental fitting into friabilator Pharma Test PTF E at 25 rpm for 4 min. After the test, weight loss was calculated. The force needed to crushed solid dental fillings was determined using texture analyzer EZ-SX, after braking a dental filling by single flat probe 10 mm diameter at a speed of 10 mm/min.

Determination of zinc ions released

The study determined the concentration of zinc ions released from the selected different types of dental fillings, using the DP ASV (differential pulse anodic stripping voltammetry) method (22, 23). Tablets prepared as dental fillings were placed in an artificial saliva solution for 2, 48 and 168 h. After this time, the solutions were decanted from above the tablets, and the concentration of zinc ions was determined using the method of anodic stripping voltammetry. The proposed voltammetric method using CGMDE allowed the determination of zinc (20 s deposition time) with LOD = 0.64 µg/L and LOQ = 1.92 µg/L. The slope of regression curve was 2.429 ± 0.036 nA/µg/L with correlation coefficients $r = 0.9997$. The precision of the method described by the RSD (relative standard deviation) of a sample was not worse than 16.58% (n = 9). The recovery of selected dental filling samples ranged from 94.7 to

Table.1. Summary of the average zinc concentration [µg/mL] in dental fillings after 2, 48 and 168 h.

Type of dental filling	2 h [µg/mL]	48 h [µg/mL]	168 h [µg/mL]
DGF (dry granulation fillings)	1.17	1.40	2.15
WGF (wet granulation fillings)	0.40	0.99	1.51
Thymodentin	36.15	55.61	73.04
Thymodentin + water	0.42	0.40	2.03
Zinc oxide	3.90	4.69	20.78
Zinc oxide-eugenol	1.13	1.28	1.30
Coltosol F®	7.28	10.36	54.52

106.5 at the level 50, 100 and 150% zinc ions. The results of zinc determination are shown in Table 1.

RESULTS AND DISCUSSION

For the development of solid dental fillings the following requirements should be considered: content uniformity of zinc ions loading in the unit, appropriate mechanical properties of tablet shaped dental fillings that provide the possibility of manual pulverization and mixing with eugenol immediately before application into teeth decay.

Preliminary studies showed that direct compression method is not appropriate in temporary solid dental filling formula development process, so the dry granulation and wet granulation manufacturing methods were chosen and developed.

For both dry granulation as well as wet granulation manufacturing process, 20 different formula compositions were verified. The best formula gained for each method composition was chosen. The final mixture obtained by wet granulation process characterized higher bulk density and better flowability properties than final mixture obtained by dry granulation method (Table 2).

Better properties, regardless qualitative composition, are caused by influence of technological process. During wet granulation increase of density is more effective than in dry granulation. Binder solution caused that particles are connected and sticking together while in granulation process, during drying stage the water evaporates. The values of Hausner ratio and compressibility index show that flowability of final mixtures are also more favorable after wet granulation process. The influence of the type of process on flowability properties is also supported by angle of repose and angle of slight values. This parameters are better for final mixture gained by wet granulation process. Improvement of mixture

properties influence on better characteristic of obtained temporary solid dental fillings.

The dental fillings obtained by dry granulation (DGF) and wet granulation (WGF) showed the differences in mechanical properties. WGF are harder and less fragile, their hardness is 32 N, in comparison to DGF characterized by hardness value 27 N. The hardness values were obtained from hardness tester. Friability of solid dental filling obtained by wet granulation method was 2.3%, dental filling manufactured by dry granulation process was completely crushed after friability study. Analysis proceeded using texture analyzer confirmed higher mechanical resistance of WGF in comparison to DGF solid dental filling. To crush this first, 3-fold higher force, with value of 150 N, should be applied. Given that developed compressed temporary solid dental fillings are going to be manually crushed and mixed with eugenol just before application into teeth, they should be soft enough. The mechanical properties of obtained solid dental fillings by both dry and wet granulation method allow to apply this procedure. They are soft enough to be manually pulverized. However, on the other hand, tableting at higher compression force to obtain harder dental fillings may be difficult because of capping occurred during the process.

Except of physical properties differences, solid dental fillings were also characterized by different amount of zinc ions dissolved into the artificial saliva solution which was also depending on the manufacturing method. The highest concentration was determined in the case of tablets made by dry granulation, incubated in artificial saliva for 168 h - it was 2.15 µg/mL dissolved. The quantity of zinc in the case of identical incubation time for the fillings prepared by wet granulation was nearly 1.5 times lower. The lowest concentration was observed in the 2-h incubation tablets prepared by wet granulation

Table 2. Properties of final mixtures obtained by dry and wet granulation process.

Parameter	Granulation method	
	dry	wet
Bulk density [g/cm ³]	1.55	1.71
Tapped density [g/cm ³]	1.98	1.95
Angle of repose [°]	40	33
Angle of slight [°]	29	28
Hausner ratio	1.28	1.04
Compressibility index	21.74	12.00

and amounted to 0.40 µg/mL. In both of parts DGF and WGF was observed that zinc concentration increased with length of incubation time.

The compiled data show that the concentration of zinc in the solution above the tablets increases over time. There was a significantly smaller amount of zinc released from the formulation with water and Thymodentin compared to compressed powder Thymodentin. The reason for this may be the curing of the formulation under the influence of water. The release of zinc from the dental filling is the result of compression the zinc oxide and eugenol and is maintained at a practically constant value from the start of the test up to 168 h. For filling containing compressed zinc oxide, after 168 h, the amount of zinc released is over 5 times higher compared to the sample subjected to 2 h of incubation in a solution of artificial saliva. Significant differences in the amounts of released zinc can be explained by the formation of complexes zinc oxide - eugenol.

The biggest difference between the amount of zinc released in the initial test period - after 2 h, and the end point of time - 168 h was observed for self-hardening paste Coltosol F. The amount of released zinc from Coltosol® increased 7.5 times. After 2 h of placement of a tablet from dental filling in artificial saliva solution, the majority of zinc was released from the tablet made from formulation Thymodentin, for which the concentration became 36.15 µg/mL. The high value of the concentration of zinc was also obtained in the case of self-hardening paste Coltosol F® (7.28 µg/mL), but this value was almost five times lower than that for formulation Thymodentin. Low concentrations after 2 h was obtained for tablets made from a mixture formulation Thymodentin and water (0.42 µg/mL).

Similar conclusions can be drawn based on the analysis of the decanted solution from tableted dental fillings after 48 h. Maximum, and also comparable to the concentration of zinc ions was obtained with formulation Thymodentin (55.61 µg/mL) and self-hardening paste Coltosol F® (10.36 µg/L). The lowest concentration was determined in a solution made up from tablets from a mixture formulation Thymodentin and water (0.4 µg/mL).

For the determination of the concentration of zinc ions in the artificial saliva solution after 168 h, the highest indicated concentration in the supernatant solution was obtained for the tablets made from the Thymodentin (73.04 µg/mL). As in the case of the concentration at 2 and 48 h, high value of Zn ion concentration was also obtained for the paste Coltosol F®. For dental fillings made from

Thymodentin and water, the concentration of zinc ions was almost 36 times lower than for tablets made only from Thymodentin preparation.

The daily requirement for zinc ions is about 15 mg and the potential toxic effect is observed after 1 g of zinc supplementation adopted for a long time (which could be observed in the case of dental fillings, usually applied through time over two weeks).

CONCLUSION

Tableting process is suitable for manufacturing temporary solid dental fillings, that may be used in dental application, after wet granulation. Suitable physical parameters provide solid dental filling useful in dental practice. Additionally, defined content of zinc ions allows to determinate the volume of eugenol that should be used to *ex tempore* preparation of solid dental fillings that cause the repeatability of amount of zinc oxide and eugenol applied into tooth. In proposed method, differences and variability appearing from experience of person preparing temporary solid dental filling are going to be eliminated. Also, taking into consideration non unified shape of ready dental fillings in a tooth, tablets of a bound temporary dental filling mixture were used for its qualitative and quantitative composition.

REFERENCES

1. Çolak H., Dülgergil Ç.T., Dalli M., Hamidi M.M.: J. Nat. Sci. Biol. Med. 4, 29 (2013).
2. Dye B.A., Tan S., Smith V., Lewis B.G., Barker L.K. et al.: Vital Health Stat. 11, 1 (2007).
3. Benjamin R. M.: Public Health Rep. 125, 158 (2010).
4. Imura N., Otani S.M., Campos M.J., Jardim Jr E.G., Zuolo M.L.: Int. Endod. J. 30, 381 (1997).
5. Ilewicz L.: Filling materials in modern restorative dentistry. Alfa-medica Press, Bielsko-Biała 2003 (in Polish).
6. Jańczuk Z.: Conservative dentistry, a clinical overview (Stomatologia zachowawcza. Zarys kliniczny). PZWL, Warszawa 2006 (in Polish).
7. Pytko-Polończyk J., Krywult A.: Temporary fillings and adjunctive materials used in karyology – compendium (Kompendium materiałów do wypełnień tymczasowych i preparatów pomocniczych stosowanych w kariologii). ZOZ Ośrodek UMEA Shinoda-Kuracejo, Kraków 2011 (in Polish).
8. Yoshihisa Y., Shimizu T.: Dermatol. Res. Pract. 2012 Article ID 749561, (2012).
9. Bjørndal L.: J. Endod. 34, 29 (2008).

10. Modena K.C.S., Casas-Apayco L.C., Atta M.T., Costa C.A.S., Hebling J. et al.: *J. Appl. Oral Sci.* 17, 544. (2009)
11. Olsson H.: *Int. Endod. J.* 39, 429 (2006).
12. Pinto K.T., Stanislawczuk R., Loguercio A.D., Grande R.H.M., Bauer J.: *Rev. Port. Estomatol. Med. Dent. Cir. Maxilofac.* 55, 83 (2014).
13. Madarati A., Rekab M.S., Watts D.C., Qualtrough A.: *Aust. Endod. J.* 34, 89 (2008).
14. Ido T., Kumakiri M., Kiyohara T., Sawai T., Hasegawa Y.: *Contact Dermatitis* 47, 51 (2002).
15. Yanagi T., Shimizu T., Abe R., Shimizu H.: *Lancet* 366, 1050 (2005).
16. Shimizu T., Kobayashi S., Tanaka M.: *Clin. Exp. Dermatol.* 28, 675 (2003).
17. Opoka W., Adamek D., Płonka M., Reczyński W., Baś B. et al.: *J. Physiol. Pharmacol.* 61, 581 (2010).
18. Šantl M., Ilić I., Vrečer F., Baumgartner F.: *Int. J. Pharm.* 414, 131 (2011).
19. Herting M.G., Kleinebudde P.: *Eur. J. Pharm. Biopharm.* 70, 372 (2008).
20. Nguyen T.H., Morton D.A.V., Hapgood K.P.: *Powder Tech.* 240, 103 (2013).
21. Kumar A., Gernaey K., De Beer T., Nopens I.: *Eur. J. Pharm. Biopharm.* 85, 814 (2013).
22. Opoka W., Jakubowska M., Baś B., Sowa-Kućma M.: *Biol. Trace Elem. Res.* 142, 671 (2011).
23. Opoka W., Szłósarczyk M., Maślanka A., Piech R., Baś B. et al.: *Acta Pol. Pharm. Drug Res.* 70, 961 (2013).

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